Improving Antimicrobial Therapy in Elders

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April 2, 2014

41st

Annual Family Physician Refresher Course

Objectives

- Distinguish between symptomatic UTI and asymptomatic bacteriuria in older adults, and apply this distinction to reduce unnecessary antibiotic use.
- Estimate risk of antibiotic resistant pathogens in pneumonia in nursing home residents and identify prescribing practices for pneumonia that may contribute to unnecessary antibiotic exposure.
- Describe measures to prevent outbreaks and reduce risk of C. difficile infection in LCTFs.
- Discuss criteria to reduce the risk of antibiotic associated adverse events in elders.

URINALYSIS CHEMISTRY

COLOR	*	YELLOW	[STRW]	
APPEARANCE	*	HAZY	[CLR]	
GLUCOSE		NEGATIVE	[NEG]	
BILIRUBIN		NEGATIVE	[NEG]	
KETONES		NEGATIVE	[NEG]	
SPEC GRAV		1.020	[1.001-1.030]	
BLOOD	*	TRACE	[NEG]	
PH		6.5	[5.0-8.0]	
PROTEIN	*	TRACE	[NEG]	
UROBILINOGEN		0.2	[0.2-1.0]	e.u./dL
NITRITES		NEGATIVE	[NEG]	
LEUK EST		NEGATIVE	[NEG]	

URINE MICROSCOPIC

WBC		5 to 10	[NONE]	cells/HPF
BACTERIA	*	TRACE	[NONE]	
RBC		1 to 2	[NONE]	cells/HPF
EPI CELLS	*	RARE	[NONE]	cells/LPF
MUCOUS	*	MODERATE	[NONE]	
HYALINE CAST		0 to 2	[NONE]	/LPF
YEAST	*	1+	[NONE]	/HPF

URINE CULTURE
SETUP: 03/28/2009 1049

SPECIMEN DESCRIPTION	CLEAN CATCH
SPECIAL REQUESTS	NONE
COLONY COUNT	EQUAL TO OR GREATER THAN 100,000 CFU/ML
CULTURE	MANY GRAM NEGATIVE RODS ID AND SENSITIVITY TO FOLLOW MODERATE GRAM NEGATIVE RODS 2 ID AND SENSITIVITY TO FOLLOW
REPORT STATUS	PENDING

American Geriatrics Society Identifies Five Things That Healthcare Providers and Patients Should Question

#4. Do not use antimicrobials to treat bacteriuria in older adults unless specific urinary tract symptoms are present.

-AGS Choosing Wisely Workgroup

J Am Geriatr Soc 61:622–631, 2013.

Prevalence of Asymptomatic Bacteriuria in Older Populations

	Prevalence (%)	
Population	Women	Men
Community	9-33	2.4-13
Institutionalized	17-55	15-37

Yoshikawa, 1996

Reasons to avoid antibiotic treatment of asymptomatic bacteriuria

- Doesn’t reduce mortality
- NNH=3[1]
- Increased antibiotic resistance

[1]Nicolle et al. *Am J Med.* 1987.

Prospective randomized studies of treatment of asymptomatic bacteriuria

Author	Subjects	Intervention	Outcome
Nicolle et al, NEJM 1983	36 Men > 80 yr NH residents	Randomized to abx vs none. Duration 2 years	No difference in: Mortality Infectious morbidity
Nicolle et al, Am J Med 1987	50 women 83 yr NH residents	Randomized to abx vs none Duration 1 year	No difference in: Mortality GU morbidity Increased AE and resistance in treated group
Abrutyn et al, Ann Intern Med 1994	358 women, 82 yr Apartment and NH	Randomized to abx vs none Duration 8 years	No survival benefit in treatment group
Ouslander et al, Ann Intern Med 1995	71 women and men 85 yr NH	Randomized to abx vs placebo 4 weeks	No difference in chronic urinary inc symptoms

Juthani-Mehta M. *Clin Geriatr Med*, 2007

Clinical symptoms of UTI

- Frequency
- Urgency
- Dysuria
- New incontinence
- CVA or suprapubic tenderness

Altered clinical presentation of infection in older persons

- Blunted fever response (1/3 without fever)
- Mental status changes (acute)
- Anorexia, malaise, weakness (new)
- Falls (acute)
- Incontinence (new)
- Functional decline (change)

Clinical features in NH residents attributed to “suspected UTI”

- Prospective cohort study in women and men
- 5 Connecticut nursing homes
- Clinically “suspected UTI”
  - Staff responses (symptoms)
  - Urinalysis/urine culture
- Multivariable regression model

Juthani-Mehta M et al. *J Am Geria Soc*, 2009.

Clinical features in NH residents attributed to “suspected UTI”

Change in mental status	156 (39.1%)
Change in behavior	76 (19.0%)
Change in character of urine	62 (15.5%)
Fever or chills	51 (12.8%)
Change in gait or fall	35 (8.8%)
Dysuria	31 (7.8%)
Change in voiding pattern	28 (7.0%)
Flank pain	23 (5.8%)
Patient or family request	15 (3.8%)
Change in functional status	10 (2.5%)
Malaise	5 (1.3%)

Juthani-Mehta M et al. *J Am Geria Soc*, 2009.

Clinical features in NH residents attributed to “suspected UTI”

- 399 “suspected UTI” episodes
  - 240/551 subjects with at least one “suspected UTI”
- Majority had negative UA (<10 WBC, $<10^5$ cfu)
  - 252/399 (63%)
- Absence of dysuria identified subjects at low risk for abnormal UA

Clinical features in NH residents attributed to “suspected UTI”

- Conclusions
  - Staff are indiscriminant in diagnosing UTI when clinical deterioration is identified in NH residents.
  - A wide spectrum of nonspecific clinical symptoms are misinterpreted as UTI.
  - Alternate diagnoses are likely overlooked.

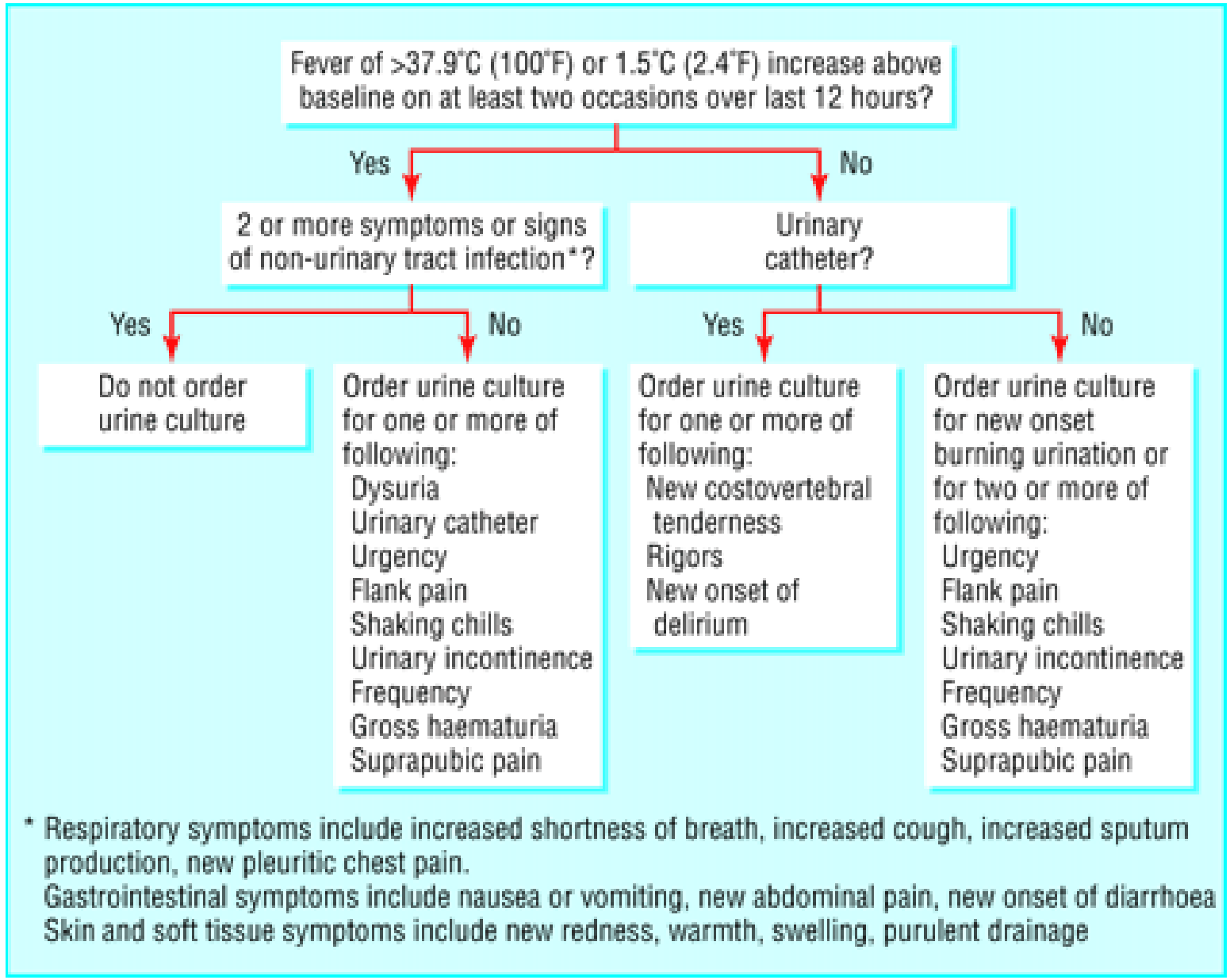
Juthani-Mehta M et al. *J Am Geria Soc*, 2009.
Nicolle L. *J Am Geria Soc*, 2009.

Minimum criteria for initiation of empiric antibiotics for UTI in LTCF

- UTI with no catheter
  - Acute dysuria or
  - Fever and one GU symptom
    - New urgency, frequency, suprapubic pain, gross hematuria, CVA tenderness or urinary incontinence
- UTI with catheter
  - One symptom of:
    - Fever
    - CVA tenderness
    - Rigors
    - Delirium

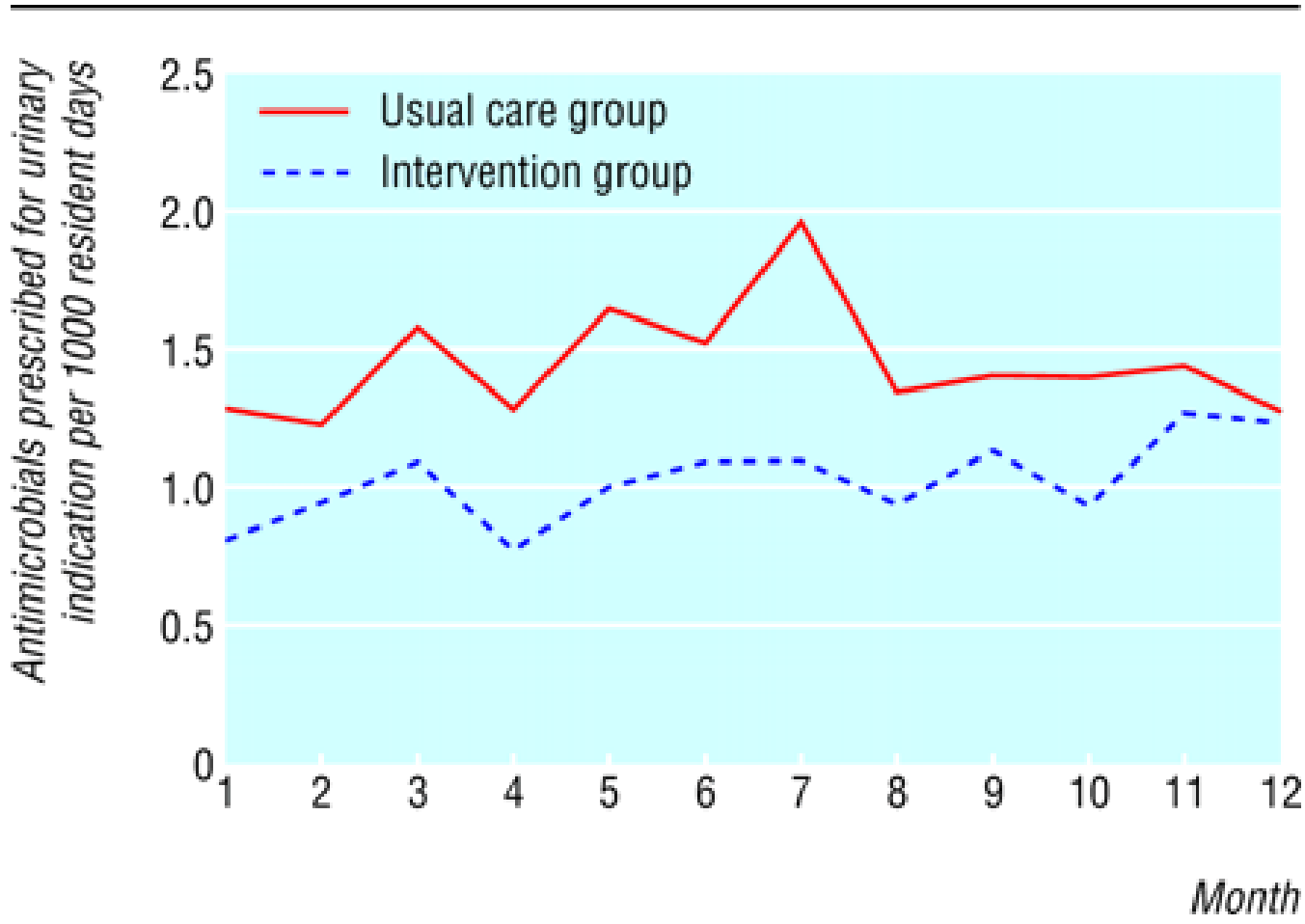
Loeb M et al. *Infect Control Hosp Epidemiol*, 2001

Multifaceted intervention to reduce antimicrobial use for "suspected UTI" in LTCF



Loeb M et al. *BMJ.* 2005.

Multifaceted intervention to reduce antimicrobial use for “suspected UTI” in LTCF



Loeb M et al. *BMJ.* 2005.

Summary: UTI overdiagnosis and overtreatment

- UTI incorrectly diagnosed in 40% of hospitalized older adults[1]
- "UTIs" account for 30-56% of antibiotic scripts written in nursing homes[2]
- Adverse outcomes of overtreatment
  - Emerging antibiotic resistance
  - Increased prevalence of health-care associated *C. difficile* infections

[1]Woodford HJ et al. *J Am Geriatr Soc*. 2009
[2]Loeb et al. *BMC Health Services Research.* 2002

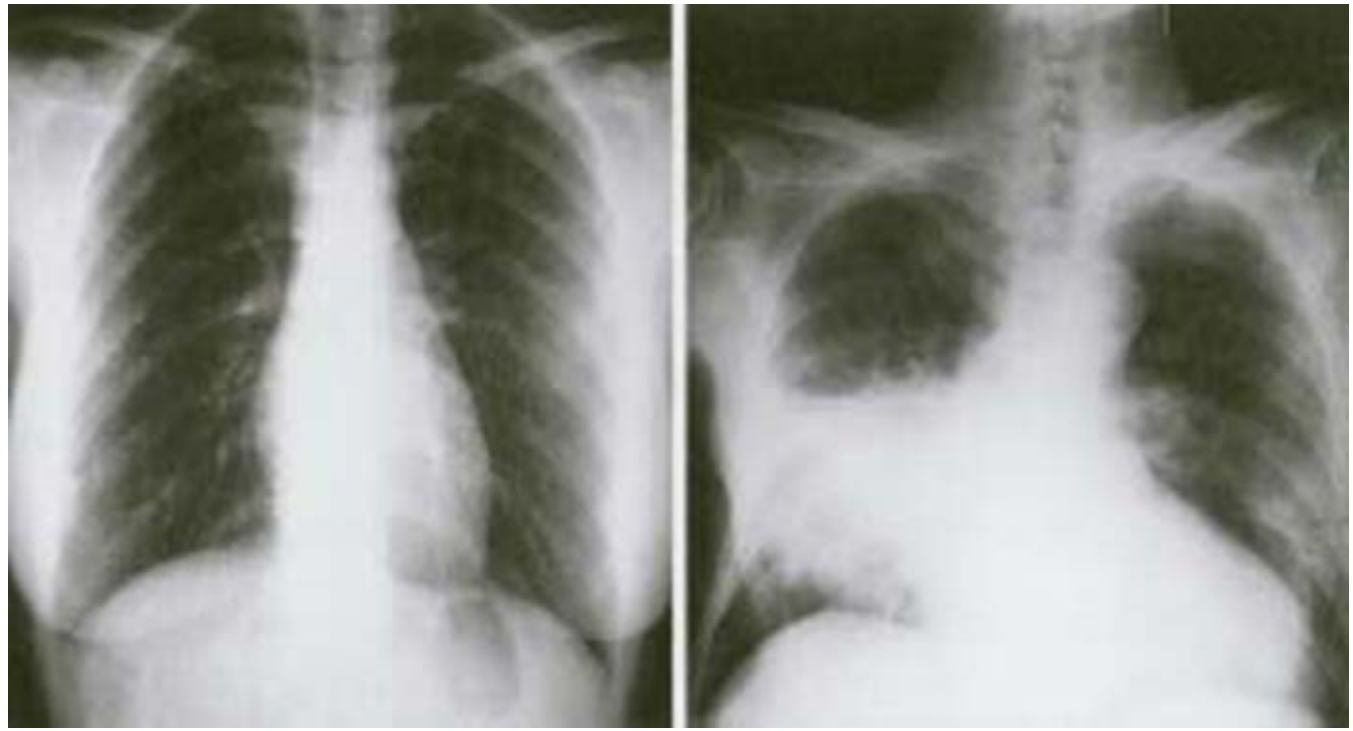
Case 2

--83 year old NH resident with dementia.

--2 day history of fever, lethargy and recent fall in room.

--IPOST: IV antibiotics acceptable. May transfer to improve comfort.

--VS: 97.7-16-76-105/72. O2 sat 92% RA.



IDSA/ATS guideline recommendations for treatment of CAP

4. Use severity-of-illness scores:

CURB-65 criteria

(confusion, uremia, respiratory rate, low blood pressure, age >65 years)

or prognostic models:

Pneumonia Severity Index (PSI)

to identify patients with CAP who may be candidates for outpatient treatment. (Strong recommendation; level I evidence.)

Mandell et al. *Clin Infect Dis.* 2007;44:S27-72.

Criteria for severe community-acquired pneumonia.

Minor criteria[a]
Respiratory rate[b] ⩾30 breaths/min
PaO_2/FiO_2 ratio[b] ⩽250
Multilobar infiltrates
Confusion/disorientation
Uremia (BUN level, ⩾20 mg/dL)
Leukopenia[c] (WBC count, <4000 cells/mm^3)
Thrombocytopenia (platelet count, <100,000 cells/mm^3)
Hypothermia (core temperature, <36°C)
Hypotension requiring aggressive fluid resuscitation
Major criteria
Invasive mechanical ventilation
Septic shock with the need for vasopressors

NOTE. BUN, blood urea nitrogen; PaO_2/FiO_2, arterial oxygen pressure/fraction of inspired oxygen; WBC, white blood cell.

[a] Other criteria to consider include hypoglycemia (in nondiabetic patients), acute alcoholism/alcoholic withdrawal, hyponatremia, unexplained metabolic acidosis or elevated lactate level, cirrhosis, and asplenia.

[b] A need for noninvasive ventilation can substitute for a respiratory rate >30 breaths/min or a PaO_2/FiO_2 ratio <250.

[c] As a result of infection alone.

Mandell L A et al. *Clin Infect Dis*. 2007;44:S27-S72

IDSA/ATS guideline recommendations for treatment of CAP

16. Presence of comorbidities

chronic heart, lung, liver, renal disease, diabetes mellitus; immunosuppressing conditions or use of immunosuppressing drugs; use of antimicrobials within the previous 3 months

other risks for drug resistant infection then treat with:

A. Respiratory fluoroquinolone (moxifloxacin, gemifloxacin, or levofloxacin)

B. β-lactam **plus** a macrolide

-High-dose amoxicillin [e.g., 1 g 3 times daily] or amoxicillin-clavulanate [2 g 2 times daily] or

-Ceftriaxone, cefpodoxime, and cefuroxime [500 mg 2 times daily];
-Doxycycline [level II evidence] is an alternative to the macrolide.

Mandell et al. *Clin Infect Dis.* 2007;44:S27-72.

Health care-associated pneumonia (HCAP) risk factors

- Hospitalization for more than 2 days in an acute care hospital in the last 90 days
- Residence in a skilled nursing facility
- Recent IV antibiotic therapy, chemotherapy, or wound care in the last 30 days
- Attending a hospital or hemodialysis clinic
- Immunosuppression

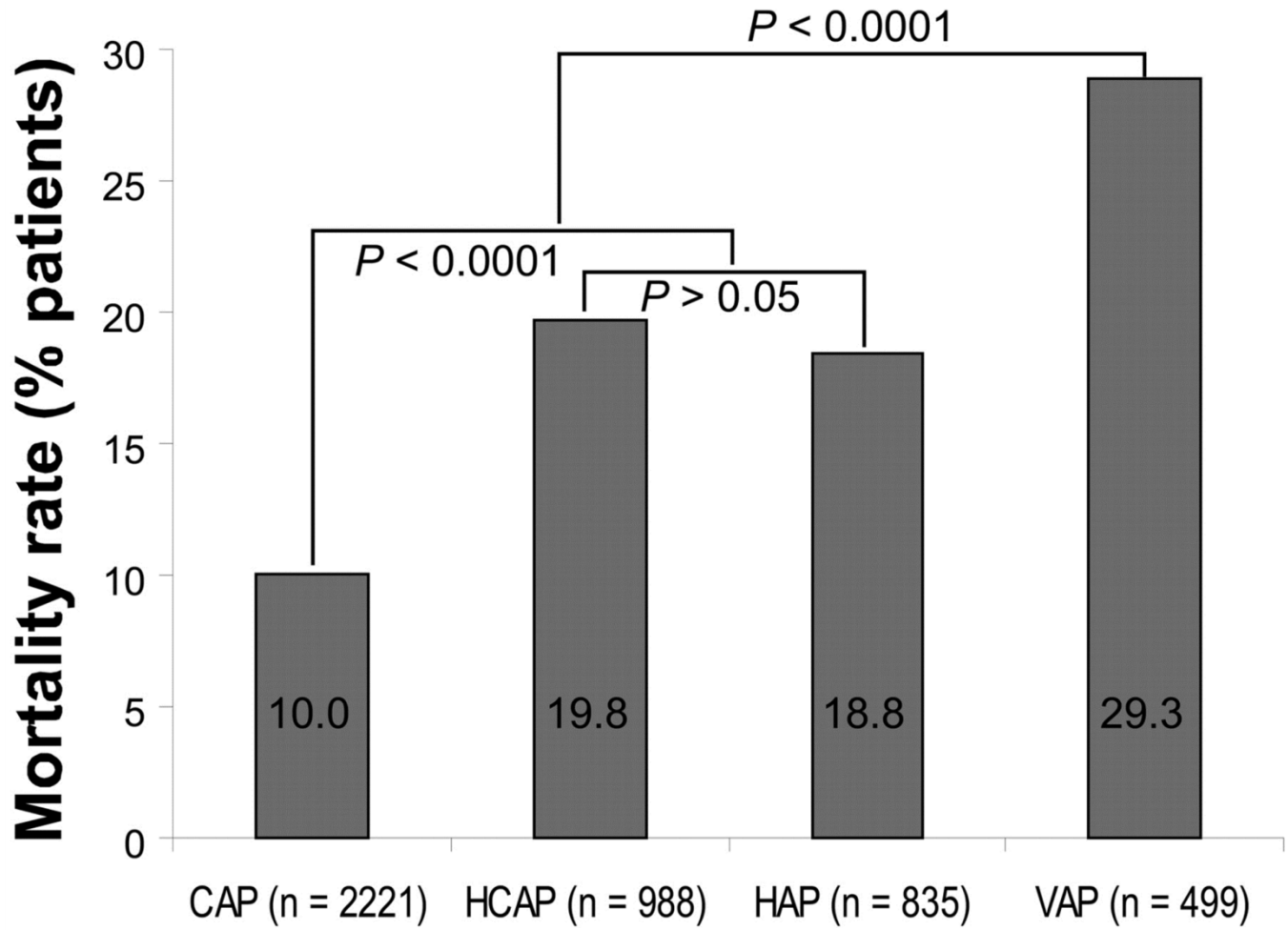
ATS,IDSA. Guidelines for the management of adults with hospital-acquired, ventilator-associated and healthcare-associated pneumonia. *Am J Respir Crit Care Med,* 2005.

Antibiotics for empiric therapy of healthcare-associated pneumonia in patients with risk factors for multidrug-resistant pathogens

Antibiotic	Dosage
Antipseudomonal cephalosporin	
Cefepime	1–2 g every 8–12 h
Ceftazidime	2 g every 8 h
Carbepenems	
Imipenem	500 mg every 6 h or 1 g every 8 h
Meropenem	1 g every 8 h
β-Lactam/β-lactamase inhibitor	
Piperacillin–tazobactam	4.5 g every 6 h
Aminoglycosides	
Gentamicin	7 mg/kg per d†
Tobramycin	7 mg/kg per d†
Amikacin	20 mg/kg per d†
Antipseudomonal quinolones	
Levofloxacin	750 mg every d
Ciprofloxacin	400 mg every 8 h
Vancomycin	15 mg/kg every 12 h‡
Linezolid	600 mg every 12 h

American Journal of Respiratory and Critical Care Medicine, Vol. 171, No. 4 (2005), pp. 388-416.
doi: 10.1164/rccm.200405-644ST

Mean mortality rate is patients with pneumonia



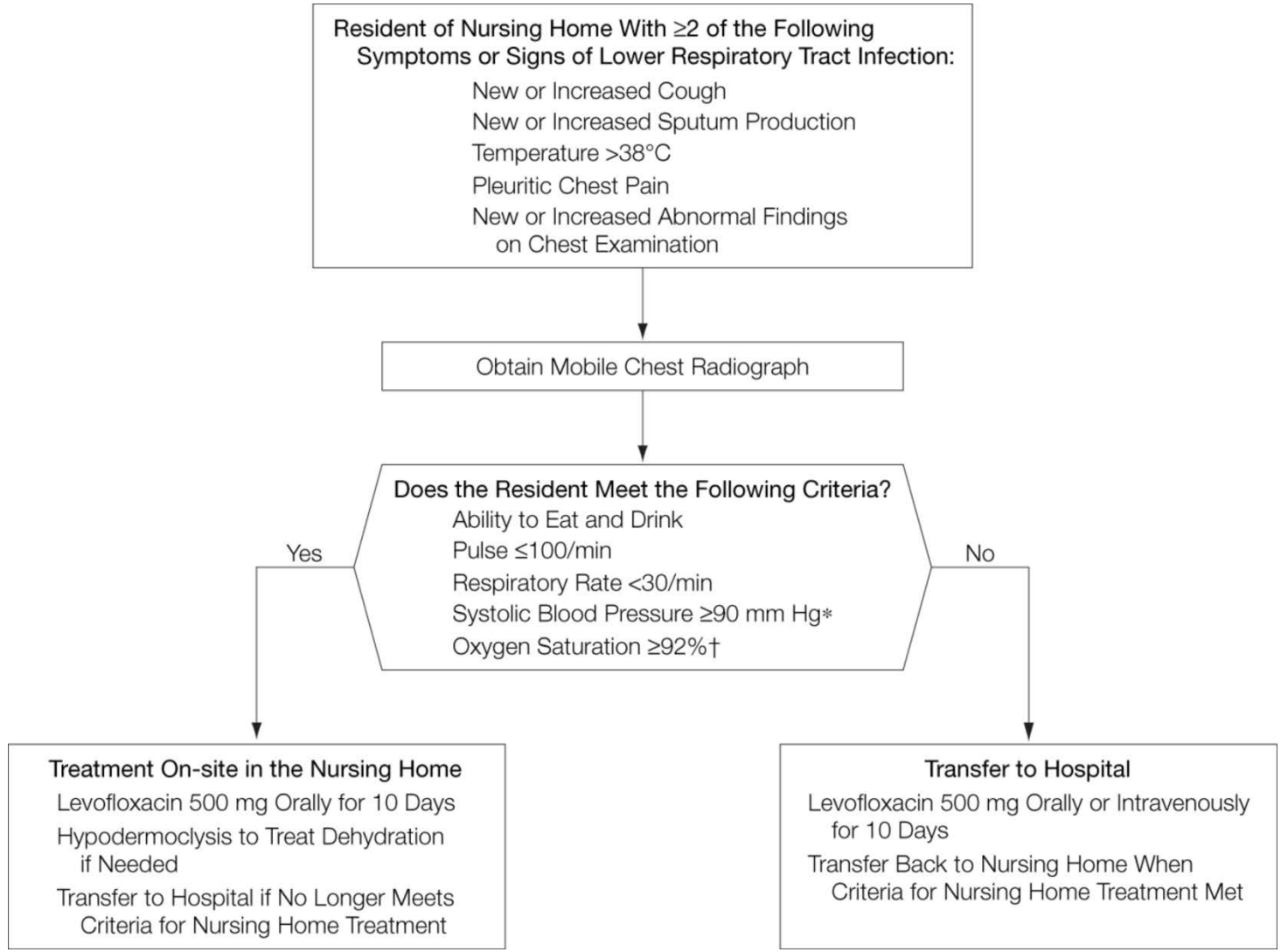
***Chest*. 2005;128(6):3854-3862. doi:10.1378/chest.128.6.3854**

Microbiology of pneumonia

Pathogen, %	CAP	HCAP	HAP	VAP
S aureus	25.5	46.7	47.1	42.5
MRSA	8.9	26.5	22.9	14.6
S pneumoniae	16.6	5.5	3.1	5.8
Pseudomonas	17.1	25.3	L18.4	21.2

***Chest.* 2005;128(6):3854-3862.**

From: **Effect of a Clinical Pathway to Reduce Hospitalizations in Nursing Home Residents With Pneumonia: A Randomized Controlled Trial**



JAMA. 2006;295(21):2503-2510. doi:10.1001/jama.295.21.2503

From: Effect of a Clinical Pathway to Reduce Hospitalizations in Nursing Home Residents With Pneumonia: A Randomized Controlled Trial

Table 2. Summary of Weighted Outcome Variables and the Differences in 10 Clinical Pathway and 9 Usual Care Nursing Homes*

Outcomes	Weighted Mean (95% CI)			*P* Value
	Clinical Pathway (n = 314)	Usual Care (n = 347)	Difference	
Hospitalizations, %†	8 (4 to 12)	20 (15 to 26)	12 (5 to 18)	.001
Hospital days per resident	0.79 (0.45 to 1.13)	1.74 (1.17 to 2.3)	0.95 (0.34 to 1.55)	.004
Visits to emergency department without admission, %	1.2 (–0.2 to 2.5)	1.6 (–0.6 to 3.8)	0.4 (–1.9 to 2.8)	.72
Death, %	3.1 (–0.2 to 6.4)	6.0 (1.8 to 10.3)	2.9 (–2.0 to 7.9)	.23
Change in quality of life from baseline	–0.032 (–0.044 to –0.019)	–0.037 (–0.050 to 0.023)	–0.005 (–0.022 to 0.012)	.055
Change in functional status from baseline	–0.105 (–0.188 to –0.022)	–0.175 (–0.389 to 0.040)	–0.069 (–0.263 to 0.124)	.23
Falls, %	10.9 (6.4 to 15.3)	9.5 (5.9 to 1.3)	–1.3 (–6.6 to 3.9)	.60
Time to normalization of vital signs, d‡	2.55 (1.60 to 3.48)	2.66 (2.24 to 3.08)	0.12 (–0.78 to 1.02)	.79

Abbreviation: CI, confidence interval.

*No residents met eligibility criteria for enrollment in 1 usual care nursing home. Differences may not be exact due to rounding.

†Based on residents in whom complete 30-day follow-up was obtained (314 [96%] of the 327 residents in the clinical pathway group and 347 [98%] of the 353 residents in the usual care group). Rates of hospitalization in the clinical pathway group were 6 of 43 (14%), 4 of 26 (15%), 6 of 50 (12%), 1 of 21 (5%), 3 of 20 (15%), 1 of 33 (3%), 2 of 5 (40%), 6 of 37 (16%), 2 of 43 (5%), and 3 of 36 (8%) for residents in each of the 10 nursing homes; and in the usual care group, rates were 6 of 43 (14%), 14 of 43 (33%), 11 of 43 (26%), 7 of 36 (19%), 10 of 53 (19%), 2 of 24 (8%), 7 of 23 (30%), 8 of 30 (27%), and 11 of 52 (21%) for residents in each of the 9 nursing homes.

‡Defined as heart rate of 100/min or less, systolic blood pressure of at least 90 mm Hg, respiratory rate of 24/min or less, and temperature of 37.2°C or less.

JAMA. 2006;295(21):2503-2510. doi:10.1001/jama.295.21.2503

Summary: Nursing home acquired pneumonia may be treated without hospitalization according to a clinical pathway.

- Broad-spectrum antibiotic therapy
  - Hospitalization within 90 days
  - Recent antibiotic therapy within the last 30 days
  - Severity of pneumonia
  - Immunosuppression
  - Poor functional status
- Appropriate monotherapy
  - Not seriously ill
  - No risk factors

Case 3

--90 year old NH resident with dementia complicated by behavior changes on 3rd course of quinolone for "UTI"

--Watery diarrhea, anorexia and recurrent fever

--VS 100.7-30-120-88/60.

C. difficile in LTCFs

- Prevalence 14.7%
- Incidence 0.2-2.6 per 1000 resident days
- Major risk for acquisition
  - Preceding antibiotic use
  - Functional disability
  - Gastrostomy feeding tube
  - Acid suppressant medications

Simor AE. *J Am Geria Soc* 58:1556-1564, 2010.

C. difficile clinical features and complications

- Onset during or within 8 weeks of antibiotics
- Watery diarrhea, abdominal cramps, fever
- Fulminant pseudomembranous colitis may be life-threatening.
- 15-35% recurrence rate within 2 months
  - Relapse (same strain)
  - Recurrence (new strain)

C. difficile diagnosis and treatment

- Test for *C. diff* toxin only on diarrheal stool
- Do not test for cure
- Discontinue inciting antimicrobial agent as soon as possible
- Avoid use of antiperistaltic agents
- Metronidazole is the drug of choice for initial episode of mild-to – moderate CDI.
  - Metronidazole 500 mg TID for 10-14 days (mild, moderate disease)
  - Vancomycin 500 mg QID with or without IV metronidazole 500 mg q 8 hrs (severe, complicated CDI)
- Same regimen as for initial episode for first recurrence
  - Do not use metronidazole beyond first recurrence or for long-term chronic therapy
  - Vancomycin taper or pulse regimen (Second or later recurrence)

SHEA-IDSA guideline. *Infect Control Hosp Epidemiol* 2010: 31: 431-455.

Measures to reduce Rick of C. difficile acquisition and transmission in LTCFs

- Surveillance
  - Test for toxin only on diarrheal specimens
  - Test should not be performed to identify asymptomatic carriers
- Barrier precautions
  - Private room/commode/dedicated patient care equipment
  - Hand hygiene with soap and water after glove removal
- Environmental cleaning/disinfection
  - Clean with diluted hypochlorite solution
- Antimicrobial use and other measures
  - Antibiotic stewardship programs

CDI and interventions to improve antibiotic prescribing

- Climo et al, *Ann Intern Med*, 1998.
  - Restriction of clindamycin in hospital
  - 11.5 CDI cases/month vs. 3.33 cases/month P < .001
  - Incidence of CDI was increasing by 2.9 cases per quarter before restriction protocol.

Davy P et al. *Cochran Database Syst Rev* 2005.

CDI and interventions to improve antibiotic prescribing

- Carling et al, *Infect Control Hosp Epidemiol* 2003.
  - Antimicrobial management team
    - Targeted 3rd gen cephalosporins and aztreonam
    - Stopped therapy after 2-3 days if no confirmed infection
    - Switched from IV to oral formulations
  - No impact on prevalence of VRE
  - No impact on prevalence of MRSA
  - Significant reduction in rate of CDI (P=.002)
  - Significant reduction in rate of antibiotic resistant GNRs

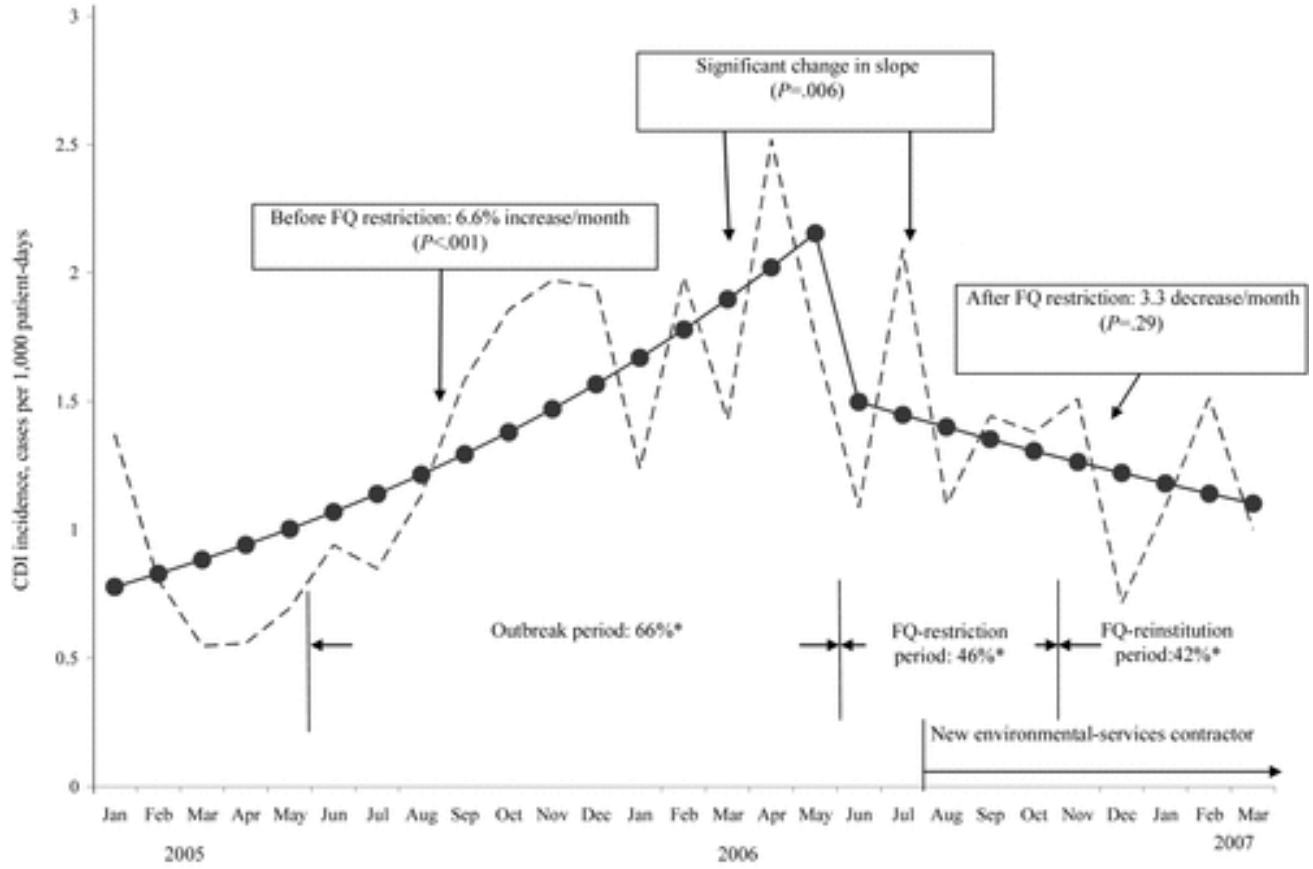
Davy P et al. *Cochran Database Syst Rev* 2005.

Fluoroquinolone resistant NAP1/BI/027 *C. diff*

- Global emergence since highly publicized outbreaks in US and Canada in 2005.
- More severe disease, higher 14 day mortality.
- Two genetically distinct lineages
  - Identical mutation (Thr82Ile) in the DNA gyrase subunit A gene *gyrA*
  - High-level fluoroquinolone resistance
- Possible control with fluoroquinolone restriction

Nat Genet, **2013**;45:109-13; *Infect Control and Hosp Epidemiol*, **2009**;30:264-72.

Figure 1. Rate of hospital-onset *Clostridium difficile* infection (CDI; *dashed line*), rate of hospital-onset CDI predicted from an interrupted time-series model *(solid line),* and percentage of *C. difficile* isolates recovered that were the epidemic strain *(asterisks),* January 2005-March 2007. A total of 61 isolates were tested during the outbreak period (June 2005-May 2006); 33, during the FQ-restriction period (June-Oct 2006); and 24, during the FQ-reinstitution period (Nov 2006-Mar 2007). FQ, fluoroquinolone.



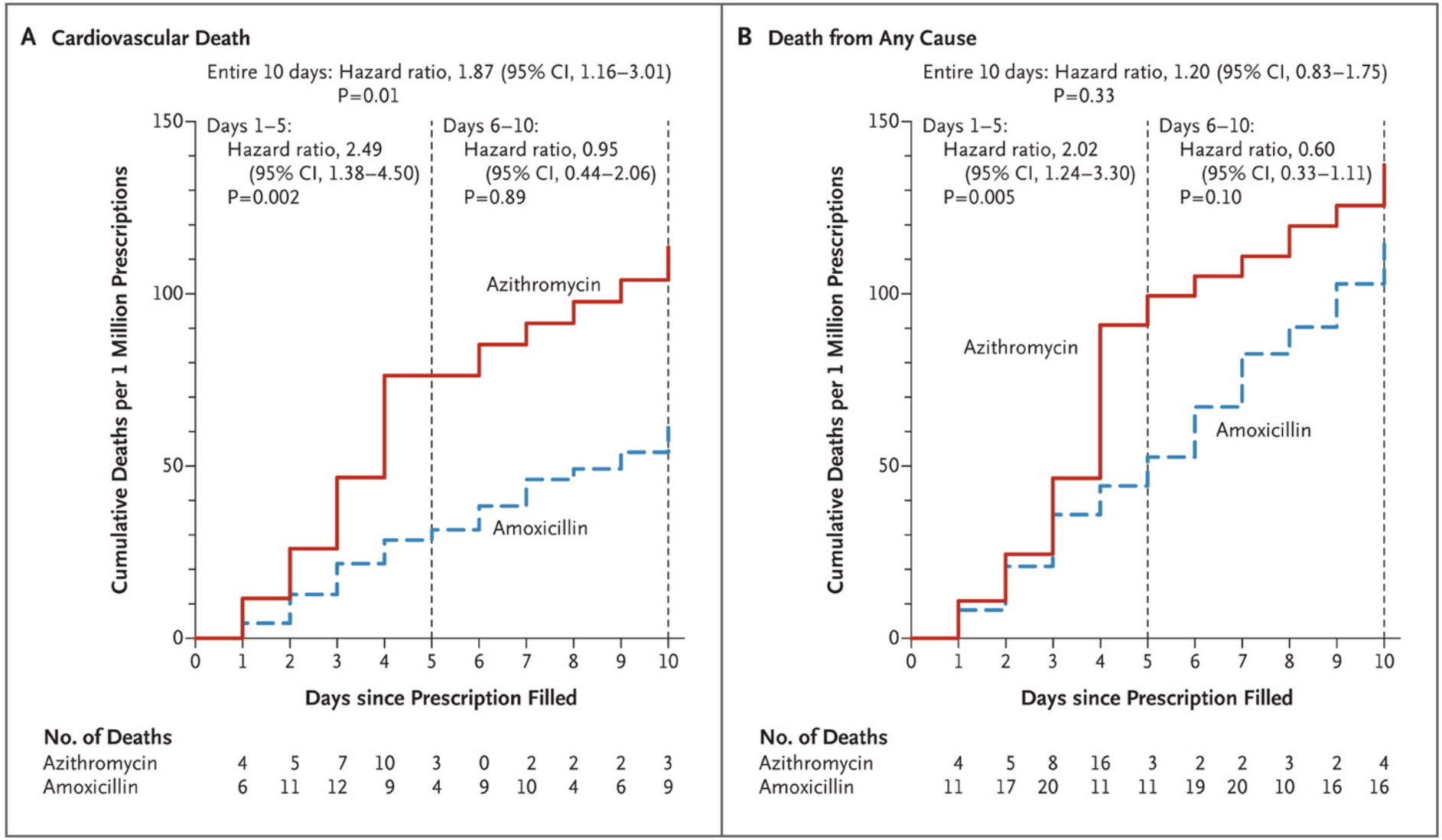
Kallen et al. *Infect Control and Hosp Epidemiol*, **2009**;30:264-72.

2012 American Geriatrics Society Beers Criteria for Potentially Inappropriate Medication Use in Older Adults

Anti-infective	Rationale	Recommendation	Quality of Evidence	Strength
Nitrofurantoin	Potential for pulmonary toxicity; safer alternatives available; lack of efficacy in patients with CrCl < 60 mL/min due to inadequate drug concentration in the urine	Avoid for long-term suppression; avoid in patients with CrCl < 60 mL/min	Moderate	Strong

The American Geriatrics Society 2012 Beers Criteria Update Expert Panel (2012), *Journal of the American Geriatrics Society*, 60: 616–631. doi: 10.1111/j.1532-5415.2012.03923.x

Azithromycin and the risk of cardiovascular death



Ray WA et al. *N Engl J Med* 2012; 366:1881-1890: 10.1056/NEJMoa1003833

2013 FDA warning

- Consider the risk of torsades de pointes and fatal arrhythmia when prescribing azithromycin or alternative antibacterial drugs. Groups at higher risk include:
  - Patients with known prolongation of the QT interval, a history of torsades de pointes, congenital long QT syndrome, bradyarrhythmias, or uncompensated heart failure
  - Patients on drugs known to prolong the QT interval
  - Patients with hypokalemia or hypomagnesemia, clinically significant bradycardia, or receiving Class IA or Class III antiarrhythmic agents.
  - Elderly patients and patients with cardiac disease may be more susceptible to the effects of arrhythmogenic drugs on the QT interval.
- The potential risk of QT prolongation should be placed in appropriate context when choosing an antibacterial drug: Alternative drugs in the macrolide or fluoroquinolone drug classes also have the potential for QT prolongation or other significant side effects that should be considered when choosing an antibacterial drug.

Additional Reading

1. High KP et al. Clinical Practice Guideline for the Evaluation of Fever and Infection in Older Adult Residents of Long-Term Care Facilities: 2008 Update by the Infectious Diseases Society of America. *Clin Infect Dis 2009*; 48:149-71.
2. Loeb M, Bentley DW, Bradley S, et al. Development of minimum criteria for the initiation of antibiotics in residents of long-term-care facilities: results of a consensus conference. *Infect Control Hosp Epidemiol* 2001;22:120-4.
3. Nicolle LE. Urinary tract infection in long-term care facility residents. *Clin Infect Dis* 2000;31:757-61.
4. Smith PW, Bennett G, Bradley S, et al. SHEA/APIC Guideline: Infection Prevention and Control in the Long-Term Care Facility. *Infect Control Hosp Epidemiol* 2008;29:785-814.
5. Loeb M, Brazil K, Lohfeld L, et al. Effect of a multifaceted intervention on the number of antimicrobial prescriptions for suspected urinary tract infections in residents of nursing homes: cluster randomized controlled trial. *BMJ.* 2005:331(7518):669-673.